Wide implications of a trial on pitolisant for cataplexy

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Pitolisant improves cataplexy: implications for clinicians, politicians, and scientists

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Narcolepsy type 1 is a neurological sleep-wake disorder with severe impact on daily life, not only because of incapacitating sleepiness during daytime, but also because patients may suffer from cataplexy, i.e. partial or even generalized voluntary muscle tone loss upon emotions. The pathophysiological hallmark of the disease is an almost complete loss of wake-promoting hypothalamic hypocretin (orexin) neurons. The choice of treatments for affected patients is limited to few stimulants, antidepressants and sodium oxybate. Recently, together with international scientific collaborators, a French company provided evidence that pitolisant, a histamine H3-receptor inverse agonist, improves subjective daytime sleepiness in narcolepsy patients.[1] Now, some of the same authors performed another well-designed randomized, double-blind, placebo-controlled trial in 105 narcolepsy patients and found that pitolisant also reduces the average number of cataplexy attacks per week.[2] Although it remains speculative how histaminergic neurotransmission modulates the expression of cataplexy, these results are interesting as they provide further clues that the histamine system may play an important role in narcolepsy.[3]

The main limitation of the study is the fact that the diagnosis of narcolepsy was based on criteria which lack specificity.[4] Along those, subjective sleepiness and experience of cataplexy are sufficient for diagnosing narcolepsy. That is why the authors chose to corroborate the diagnosis in a majority of patients with multiple sleep latency tests (MSLT). Still, the diagnostic value of standard MSLT is not optimal as shift work and chronic sleep deprivation can produce similar findings,[5,6] and test-retest reliability of MSLT in hypersomnia conditions is poor.[7] The fact that reported mean sleep latencies in the cohort of Szakacs et al. (4.2-4.7 minutes) were somewhat higher than reported in other cohorts including ours (2.6-2.9 minutes), leaves some uncertainty about patient inclusion. [2,8]

Even if there remain this and other minor methodological concerns, this study is important and deserves attention by clinicians, politicians, and scientists, and here is why:

First, for clinicians, this study is very good news as it will hopefully contribute to approval of this novel compound by the respective national agencies. We need more treatment options to better tailor individualized therapy for narcolepsy patients. For instance, as a subset of patients suffers from side effects of modafinil, the good tolerability makes pitolisant a very interesting compound.[1] The additional effect on cataplexy puts it even in direct competition to sodium oxybate, a nocturnal treatment option which also improves both sleepiness and cataplexy, but necessitates drug intake before and during night sleep, and closer monitoring for side effects.

Second, this study is another proof that excellent collaboration between Western and Eastern European countries is possible. The French investigators made it clear that they chose to do the study in Eastern Europe as study procedures in Western countries would have taken too long. It is a fact that ethical standards and good clinical practice procedures in Western countries became enormously laborious, expensive, time-consuming, and – as a result – even confusing, which reduces our competitiveness compared to other world regions. We must halt and reverse this development, if we want to stay on top of the game, particularly since more administration does not improve ethical handling of study procedures or care for patients.

Last but not least, this study is a good example that important findings deserve high-impact publication even if the methods have been outdated at the time of printing. The newer diagnostic criteria for narcolepsy, which were published after the present study started, are more specific, and additional studies provided even better insights into how to improve the diagnosis of narcolepsy based on sleep laboratory tests.[6,8-10] Thus, confirmatory studies on the effect of pitolisant on cataplexy shall be based

on these criteria. I still nourish some hope that such high-quality confirmatory - and also negative - studies will get similar impact and attention. Today, negative and confirmatory studies are still way too difficult to publish. We have observed this *in extremis* some years ago: when we finally found a journal to report that we could by no ways replicate a previous finding published in a leading journal of the respective field, we got feedbacks from 14 other groups worldwide.[11] They all tried to replicate the findings and spent a total of 6.5 million USD in vain, but found it too ungrateful to publish their negative results.

Altogether, let us wait for this promising compound to be available for patients, let us welcome confirmatory studies on the multiple effects of pitolisant, and let us engage ourselves in speaking up for better conditions to perform and publish such studies.

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